REMARKS

The Office Action of March 14, 2003 presents the examination of claims 30-36. These claims remain pending. New claim 37 is added for examination.

Request for initialed form PTO-1449

The Examiner has not yet provided any acknowledgment of Applicants' IDS filed June 4, 2002. The Examiner is respectfully requested to send an initialed form PTO-1449 indicating consideration of the reference sent with that paper as part of the next communication from the Office.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 30-33, 35 and 36 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support for the recitation of "atelocollagen" in the claims. The Examiner indicates that this recitation is deemed new matter.

The Examiner is referred to Examples 6 and 7 of the specification, at page 26. Both of these working examples utilize atelocollagen in the formulation of a gel or sponge (see original claim 8). Thus, the recitation of "atelocollagen" as an ingredient of a formulation of the invention is not new matter and the instant rejection should be withdrawn.

Rejection over prior art

Claims 30-33

Claims 30-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Szoka et al., WO '265 in view of Fujioka et al., US '704 and Bonadio et al., US '416. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that the Examiner is using improper hindsight reconstruction of the invention from the prior art, using the present claims as a template upon which to assemble disclosure of each ingredient of the claimed formulation from the prior art. Such an approach to making a rejection for obviousness is improper and therefore the present rejection should not stand.

Szoka discloses mixing of nucleic acids with various carbohydrate "cryoprotectants" to preserve the nucleic acid during freeze drying.

Fujioka et al. disclose mixing atelocollagen with protein macromolecules to formulate a sustained release composition. Citric acid or various amino acids are also included in the formulation. On the other hand, the present invention relates to formulations of nucleic acids. As Applicants have argued previously, the chemical and physical properties of proteins and

nucleic acids are very different, and these differences result in different requirements to obtain an effective sustained release formulation.

The Examiner should note, therefore, that the amounts of the amino acids used by Fujioka et al. are considerably larger than the amounts described in the present specification. The Examiner should compare the amounts at col. 2, lines 51 ff. in Fujioka et al. (5-50%) to 10 mg/ml (i.e. 1%) in the Examples of the present specification. This difference in amount serves to emphasize that differences in formulation are necessary to make compositions appropriate for proteins and appropriate for nucleic acids.

Bonadio et al. disclose formulation of nucleic acids with a "biodegradable" matrix for local application to bone. Collagen is mentioned as a possible matrix. Applicants note that the collagen employed by Bonadio is an insoluble, fibrous collagen, in contrast to the more soluble atelocollagen used in the present invention. The disclosure of Bonadio suggests that for nucleic acid applications, a sustained release formulation should be <u>insoluble</u>, *e.g.* comprising biodegradable polymers such as fibrous collagens and polylactic acid polymers, or insoluble mineral substrates such as hydroxyapatite or tricalcium phosphate. See col. 22, line 49 to col. 23, line 5. There is no motivation provided by the references or anywhere in the

record to replace the insoluble substrates of Bonadio by a soluble substrate such as atelocollagen. The allegation by the Examiner that such a replacement is an obvious substitution simply evidences the hindsight reconstruction nature of the rejection.

Applicants submit that combining the references cited by the Examiner does not result in the present invention. In particular, the result would be a formulation comprising a carbohydrate or amino acid, a protein and atelocollagen or a carbohydrate or amino acid, a nucleic acid and an insoluble collagen. There is no motivation to use a nucleic acid with an atelocollagen provided by the references. The inclusion of 5- to 50-fold more of the carbohydrate or amino acid component by Fujioka et al. further emphasizes the incompatibility of the combination of the cited references.

For all of the above reasons, the Examiner has failed to establish *prima facie* obviousness of the invention as claimed in claims 30-33 over Szoka et al., Fujioka et al. and Bonadio et al. and the instant rejection should be withdrawn.

Claims 34-36

Claims 34-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fujioka et al. US '704, in view of Bonadio et al. US '416 and Szoka et al. WO '265. This rejection

is respectfully traversed. Reconsideration and withdrawal thereof are requested.

First, Applicants submit that, as for the rejection of claims 30-33 over these references, the Examiner has improperly used hindsight reconstruction of the invention to select certain ingredients from the references and assemble them upon the claims as a template. Applicants' reasoning in this regard is explained above. The instant rejection should be withdrawn for this reason alone.

Further, Applicants have previously pointed out teachings of the specification that demonstrate that use of certain amino acids, or of citric acid or tartaric acid, provide unexpected beneficial results to a sustained release formulation of a CC plasmid DNA. (Table 3 at page 32 of the specification as noted at page 9 of Applicants' paper of January 22, 2003.) The Examiner has dismissed these data, apparently because the claimed formulation comprises atelocollagen. (*See*, page 11, lines 3-9 of the Office Action.) However, the Examiner is reminded that claim 34 does not recite atelocollagen as an ingredient and so the data in Table 3 are relevant to at least this claim.

Furthermore, Applicants provide attached the Declaration of Dr. Shunji Nagahara. Dr. Nagahara's Declaration establishes that inclusion of atelocollagen does not negate the unexpected

result shown by the data in Table 3. The data in Dr. Nagahara's Declaration show that, with atelocollagen, with or without lipid, the use of citrate and tartrate as an additive to a sustained release formulation of CC plasmid DNA provides a beneficial increase in stability of the DNA one of skill in the art would not expect from reading the references cited by the Examiner.

Applicants submit that the Declaration of Dr. Nagahara is sufficient to establish unobviousness of the invention as claimed, at least in claims 34-36, over the references cited by the Examiner. Thus, Dr. Nagahara's declaration provides an additional reason for withdrawal of the instant rejection.

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Mark J. Nuell, #36,623

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

DRN/mua
0020-4769P

Attachment: Declaration under 37 C.F.R. § 1.132